

WHAT IS CLAIMED IS:

1. A method of direct-write lithography for improving the deposition of selected protein patterning compounds comprising:  
providing a substrate surface;  
providing a tip with a selected protein patterning compound thereon;  
depositing the selected protein patterning compound from the tip to the substrate surface to produce a pattern,  
wherein the tip is modified by a selected chemical agent to improve deposition of the selected protein patterning compound to the substrate surface.
2. A method according to claim 1, wherein the chemical agent improves reproducibility.
3. A method according to claim 1, wherein the chemical agent improves scan speed.
4. A method according to claim 1, wherein the chemical agent improves resolution.
5. A method according to claim 1, wherein the tip is modified to inhibit protein adsorption.
6. A method according to claim 1, wherein the tip is modified to reduce the activation energy for protein transport from tip to surface.

7. A method according to claim 1, wherein the chemical agent is one or more low molecular weight polyalkylene glycol compounds.
8. A method according to claim 1, wherein the chemical agent is one or more silane compounds.
9. A method according to claim 1, wherein the chemical agent is electrostatically charged.
10. A method according to claim 1, wherein the chemical agent is negatively charged.
11. A method according to claim 1, wherein the chemical agent forms a self-assembled monolayer on the tip.
12. A method according to claim 1, wherein the chemical agent forms a self-assembled monolayer on the tip and is negatively charged.
13. A method according to claim 1, wherein the tip is coated with metal and the chemical agent forms a self-assembled monolayer on the metal-coated tip and is negatively charged.
14. A method according to claim 1, wherein the tip is a scanning probe nanoscopic tip.
15. A method according to claim 1, wherein the tip is an AFM tip.

16. A method according to claim 1, wherein the tip is a hollow tip.
17. A method according to claim 1, wherein the substrate surface is adapted before deposition to provide a stable protein pattern.
18. The method according to claim 1, wherein the substrate surface is adapted before deposition to covalently bond to the protein.
19. The method according to claim 1, wherein the substrate surface is adapted to chemisorb to the protein.
20. The method according to claim 1, wherein the substrate surface is adapted to electrostatically bond to the protein.
21. A method according to claim 1, wherein the pattern includes a dot.
22. A method according to claim 1, wherein the pattern includes a line.
23. The method according to claim 1, wherein the pattern includes dot diameter or line width of 1,000 nm or less.

24. The method according to claim 1, wherein the pattern includes dot diameter or line width of 500 nm or less.

25. The method according to claim 1, wherein the pattern includes dot diameter or line width of about 50 nm to about 550 nm.

26. The method according to claim 1, wherein the pattern is a dot or line one protein molecule wide and high.

27. The method according to claim 1, wherein the pattern has a height of about 8 nm to about 10 nm.

28. The method according to claim 1, wherein the protein is a simple protein.

29. The method according to claim 1, wherein the protein is a conjugated protein.

30. The method according to claim 1, wherein the protein is a globular protein.

31. The method according to claim 1, wherein the protein is a fibrous protein.

32. The method according to claim 1, wherein the protein is an enzyme.

33. The method according to claim 1, wherein the protein is a viral protein.

34. The method according to claim 1, wherein the protein is complexed with other protein, polypeptide, peptide, or nucleic acid.

35. The method according to claim 1, wherein the protein is applied to the tip using a solution of protein comprising an additive, wherein the additive improves application to the tip, improves protein deposition, or improves retention of protein biological activity upon application to the surface.

36. The method according to claim 1, wherein the relative humidity during deposition at room temperature is about 55% to about 70%.

37. The method according to claim 1, wherein the lithography is a nanolithography, the tip is an atomic force microscopic tip, the tip is modified to inhibit protein adsorption, and the chemical agent is electrostatically charged.

38. The method according to claim 37, wherein the pattern includes dot diameter or line width of 1,000 nm or less.

39. The method according to claim 38, wherein the relative humidity during deposition at room temperature is about 55% to about 70%.

40. A method of direct-write nanolithography for improving the deposition of selected peptide patterning compounds comprising:

- providing a substrate surface;
- providing a nanoscopic tip with a selected peptide patterning compound thereon;
- depositing the selected peptide patterning compound from the tip to the substrate surface to produce a pattern,

wherein the tip is modified by a selected chemical agent to improve deposition of the selected peptide patterning compound to the substrate surface.

41. A method according to claim 40, wherein the chemical agent improves reproducibility.

42. A method according to claim 40, wherein the chemical agent improves scan speed.

43. A method according to claim 40, wherein the chemical agent improves resolution.

44. A method according to claim 40, wherein the tip is modified to inhibit peptide adsorption.

45. A method according to claim 40, wherein the tip is modified to reduce the activation energy for peptide transport from tip to surface.

46. A method according to claim 40, wherein the chemical agent is one or more low molecular weight polyalkylene glycol compounds.

47. A method according to claim 40, wherein the chemical agent is one or more silane compounds.

48. A method according to claim 40, wherein the chemical agent is negatively charged.

49. A method according to claim 40, wherein the chemical agent forms a self-assembled monolayer on the tip.

50. A method according to claim 40, wherein the chemical agent forms a self-assembled monolayer on the tip and is negatively charged.

51. A method according to claim 40, wherein the tip is coated with metal and the chemical agent forms a self-assembled monolayer on the metal-coated tip and is negatively charged.

52. A method according to claim 40, wherein the nanoscopic tip is a scanning probe microscope nanoscopic tip.

53. A method according to claim 40, wherein the nanoscopic tip is an AFM tip.

54. A method according to claim 40, wherein the nanoscopic tip is a hollow tip.
55. A method according to claim 40, wherein the substrate surface is adapted to provide a stable peptide pattern.
56. The method according to claim 40, wherein the substrate surface is adapted to covalently bond to the peptide.
57. The method according to claim 40, wherein the substrate surface is adapted to chemisorb to the peptide.
58. The method according to claim 40, wherein the substrate surface is adapted to electrostatically bond to the peptide.
59. A method according to claim 40, wherein the pattern includes a dot.
60. A method according to claim 40, wherein the pattern includes a line.
61. The method according to claim 40, wherein the pattern includes dot diameter or line width of 1,000 nm or less.

62. The method according to claim 40, wherein the pattern includes dot diameter or line width of 500 nm or less.

63. The method according to claim 40, wherein the pattern includes dot diameter or line width of about 50 nm to about 550 nm.

64. The method according to claim 40, wherein the pattern is a dot or line one peptide molecule wide and high.

65. The method according to claim 40, wherein the pattern has a height of about 8 nm to about 10 nm.

66. The method according to claim 40, wherein the peptide is a simple peptide.

67. The method according to claim 40, wherein the peptide is a complex peptide.

68. The method according to claim 40, wherein the peptide comprises a protein.

69. The method according to claim 40, wherein the peptide comprises an oligopeptide.

70. The method according to claim 40, wherein the peptide comprises a polypeptide.

71. The method according to claim 40, wherein the peptide is in combination with non-peptide units.

72. The method according to claim 40, wherein the peptide comprises a single polypeptide chain.

73. The method according to claim 40, wherein the peptide comprises multiple polypeptide chains.

74. The method according to claim 40, wherein the peptide includes ten or less peptide bonds.

75. The method according to claim 40, wherein the peptide comprises at least 100 peptide bonds.

76. The method according to claim 40, wherein the peptide comprises a globular protein.

77. The method according to claim 40, wherein the peptide comprises a fibrous protein.

78. The method according to claim 40, wherein the peptide comprises an enzyme.

79. The method according to claim 40, wherein the peptide comprises a virus.

80. The method according to claim 40, wherein the peptide comprises an antibody.

81. The method according to claim 40, wherein the peptide is applied to the tip using a solution of peptide comprising an additive, wherein the additive improves application to the tip, improves peptide deposition, or improves retention of peptide biological activity upon application to the surface.

82. The method according to claim 40, wherein the relative humidity during deposition is at least 50%.

83. The method according to claim 40, wherein the relative humidity during deposition is about 55% to about 70%.

84. The method according to claim 40, wherein the tip is modified to inhibit peptide adsorption, the chemical agent is electrostatically charged, and the nanoscopic tip is a scanning probe microscope tip.

85. The method according to claim 84, wherein the relative humidity during deposition is about 55% to about 70%.

86. The method according to claim 85, wherein the peptide comprises an oligopeptide.

87. The method according to claim 40, wherein the tip is modified to inhibit peptide adsorption, the chemical agent is electrostatically charged, and the nanoscopic tip is an atomic force microscope tip.

88. The method according to claim 87, wherein the relative humidity during deposition is at least about 70%.

89. The method according to claim 87, wherein the relative humidity during deposition is about 55% to about 70%.

90. A method of direct-write nanolithography comprising:  
providing an atomic force microscopic tip modified to resist protein adsorption and which is coated with protein,  
providing a substrate comprising an electrostatically charged surface, and  
depositing the protein on the surface to form a protein pattern.

91. The method according to claim 90, wherein the tip is modified by a hydrophilic, biocompatible compound to resist protein adsorption.

92. The method according to claim 90, wherein the pattern includes a dot.

93. The method according to claim 90, wherein the pattern includes a line.

94. The method according to claim 90, wherein the pattern is an array of dots or lines.

95. The method according to claim 90, wherein the protein pattern is a monolayer of protein.

96. The method according to claim 90, wherein the protein pattern has protein features about 100 nm to about 550 nm.

97. The method according to claim 90, wherein the protein is labeled with a fluorophore.

98. The method according to claim 90, wherein the tip is modified by a hydrophilic, biocompatible compound to resist protein adsorption, and the protein pattern has protein features about 100 nm to about 550 nm.

99. The method according to claim 98, wherein the pattern is an array of dots or lines.

100. A method of nanolithography comprising:

providing a substrate;

providing a scanning probe microscope tip coated with a peptide or protein patterning compound, wherein the tip comprises a metallic surface which has been treated to promote protein or peptide coating of the tip; and

contacting the coated tip with the substrate so that the peptide or protein patterning compound is applied to the substrate so as to produce a pattern.

101. The method according to claim 100, wherein the substrate is a metal, and the peptide or protein patterning compound comprises sulfur.

102. The method according to claim 101, wherein the metal substrate is gold.

103. The method according to claim 100, further comprising the step of analyzing the pattern with use of nanoparticle probe labels.

104. The method according to claim 100, further comprising the step of analyzing the pattern with use of atomic force microscopic detection after binding the pattern to a binding moiety.

105. The method according to claim 100, wherein the scanning probe microscopic tip is part of a cantilever and the back side of the cantilever is treated so that the back side is passivated against protein or peptide adhesion.

106. The method according to claim 100, wherein the metallic surface is gold and the treatment is with a sulfur-containing compound.

107. A method according to claim 100, wherein the substrate is passivated against additional deposition of protein or peptide.

108. The method according to claim 100, wherein the substrate is passivated against additional deposition of protein or peptide, the substrate is a metal, and the peptide or protein patterning compound comprises sulfur.

109. The method according to claim 108, wherein the relative humidity during contact is at least 55%.

110. A method of direct-write nanolithography for improving the deposition of selected protein patterning compounds consisting essentially of:

providing a substrate surface;

providing a nanoscopic tip with a selected natural protein patterning compound thereon;

depositing the selected protein patterning compound from the tip to the substrate surface to produce a pattern,

wherein the tip is modified by a selected chemical agent to improve deposition of the selected protein patterning compound to the substrate surface.

111. A method for improving the deposition of selected peptide patterning compounds consisting essentially of:

providing a substrate surface;

providing a nanoscopic tip with a selected natural peptide patterning compound thereon;

depositing the selected peptide patterning compound from the tip to the substrate surface to produce a pattern by direct-write nanolithography,

wherein the tip is modified by a selected chemical agent to improve deposition of the selected peptide patterning compound to the substrate surface.

112. A method for high resolution direct-write nanolithography of peptide and protein arrays, comprising:

direct-write nanolithographic printing of the peptide or protein onto a substrate from a nanoscopic tip to provide a protein or peptide patterned array on the substrate, wherein the nanoscopic tip has been adapted for peptide or protein deposition and the array is characterized by a pattern separation distance of less than about 1,000 nm.

113. The method according to claim 112, wherein the pattern separation distance is less than about 500 nm.

114. The method according to claim 112, wherein the pattern separation distance is less than about 350 nm.

115. The method according to claim 112, wherein the array is an array of dots.

116. The method according to claim 112, wherein the array is an array of lines.

117. The method according to claim 112, wherein the nanoscopic tip is an atomic force microscope nanoscopic tip.

118. The method according to claim 112, wherein the pattern comprises dots having dot diameter of about 100 nm to about 550 nm.

119. The method according to claim 112, wherein the pattern comprises dots having a height of about 8 nm to about 10 nm.

120. A method of depositing a plurality of different protein nanoscopic deposits, comprising direct write nanolithographic writing of the protein with nanoscopic tips, wherein the average distance between the nanoscopic deposits is about 500 nm or less.

121. A method according to claim 120, wherein the average distance between the nanoscopic deposits is about 350 nm or less.

122. A method according to claim 120, wherein the average distance between the nanoscopic deposits is about 100 nm or less.

123. A method for generating protein arrays comprising depositing dots of proteins onto a substrate at a rate of at least about 85 dots per four minutes.

124. The method according to claim 123, wherein the dots have dot diameters of about 550 nm or less.

125. The method according to claim 123, wherein the dots are separated by a separation distance of about 1,000 nm or less.

126. The method according to claim 123, wherein the dots are separated by a separation distance of about 500 nm or less.

127. The method according to claim 123, wherein the dots are separated by a separation distance of about 350 nm or less.

128. The method according to claim 123, wherein the dots comprise at least two different types of proteins.

129. The method according to claim 123, wherein the dots are about 10 nm high or less.

130. A protein array comprising a plurality of protein dots, wherein the dots have a dot diameter of about 450 nm or less and a dot spacing of about 350 nm or less.

131. The protein array according to claim 130, wherein the dots have a dot diameter of about 100 nm or less and a dot spacing of about 200 nm or less.

132. The protein array according to claim 130, wherein the dots have a dot diameter of about 55 nm or less and a dot spacing of about 100 nm or less.

133. The protein array according to claim 130, wherein the plurality of dots is at least about 85 dots.

134. The protein array according to claim 130, wherein the height of the dots is about 10 nm or less.

135. The protein array according to claim 130, wherein the array comprises at least two different types of proteins.

136. The protein array according to claim 130, wherein the array comprises protein-adsorption passivated regions between the protein dots.

137. The protein array according to claim 130, wherein the array exhibits bio-recognition properties only in the protein dots.

138. The protein array according to claim 135, wherein the array exhibits selective bio-recognition properties.

139. A protein nanoarray prepared by a method comprising the method of claim 1.

140. A peptide nanoarray prepared by a method comprising the method of claim 40.